INDICATIONS CONTRA-INDICATIONS DOSAGE SIDE-EFFECTS PREGNANCY OVERDOSE
IDENTIFICATION PATIENT INFORMATION

XALATAN® Eye Drops

Logo

SCHEDULING STATUS:
S4

PROPRIETARY NAME
(and dosage form):

XALATAN® Eye Drops

COMPOSITION:
Each millilitre contains **latanoprost** 50 micrograms and benzalkonium chloride 0,02% m/v as preservative.
One drop contains approximately 1,5 micrograms latanoprost.

PHARMACOLOGICAL CLASSIFICATION:
A 15.4 Ophthalmic preparations: Other

PHARMACOLOGICAL ACTION:
Mechanism of action:
Latanoprost is a prostanoid selective prostaglandin F_2 (FP) receptor agonist, which is believed to reduce the intraocular pressure by increasing the outflow of aqueous humour. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow.
Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys.
Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment.
Animal studies:
In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The results from the pre-clinical program demonstrated that the increased pigmentation is unlikely to be associated with proliferation of melanocytes. It appears that the mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma. In ocular toxicity studies, administration of latanoprost at a dose of 6 micrograms/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect has been reversible and occurred at doses above the clinical dose level.
Pharmacokinetics
Absorption:
Latanoprost is absorbed through the cornea. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.
Metabolism:
Latanoprost, an isopropyl ester prodrug, is hydrolysed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolised by the liver to the 1,2 dinor- and 1,2,3,4-tetranor-metabolites via fatty acid beta-oxidation.
Excretion:
The elimination of the acid of latanoprost from human plasma is rapid ($t_{½}$ = 17 minutes) after both intravenous and topical administration. Systemic clearance is approximately 7 ml/min/kg. Following hepatic beta-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing respectively.

INDICATIONS:
Reduction of elevated intraocular pressure in patients with open angle glaucoma, chronic angle closure glaucoma and ocular hypertension.

CONTRA-INDICATIONS:
Known hypersensitivity to latanoprost, benzalkonium chloride or any other component in XALATAN.
Use of all contact lenses. XALATAN contains a high concentration of benzalkonium chloride, which may be absorbed by contact lenses.

WARNINGS:
XALATAN may gradually change the eye colour by increasing the amount of brown pigment in the iris. The colour change is due to increased melanin content in the stromal melanocytes of the iris and not to an increase innumber of melanocytes. The change in iris colour occurs slowly and may not be noticeable for several months to years. Before treatment is instituted, patients should be informed of the possibility of iris colour change. Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation in the treated eye, and thus heterochromia between the eyes. The increased pigmentation is irreversible.
This change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e, blue-brown, grey-brown, yellow-brown and green-brown. The onset of the change is usually within the first 8 months of treatment but may occur later in a small number of patients. The effect, based on evidence from consecutive photographs, has been seen in 30% of all patients during 4 years of treatment in clinical trials. The highest incidence was found in patients with green-brown and yellow-brown irides. In patients with homogenously blue, grey, green or brown eyes, the change has only rarely been seen. Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. No further increase in brown iris pigmentation has been observed after discontinuation of treatment.
Eyelash changes may occur.
Neither naevi nor freckles of the iris have been affected by treatment.
Accumulation of pigment in the trabecular meshwork or elsewhere in the anterior chamber has not been observed in clinical trials.
Caution is recommended when using XALATAN in aphakic or pseudophakic patients with torn posterior capsules or in patients with known risk factors for cystoid macular oedema.
Pregnancy
The safety of XALATAN for use in pregnancy has not been established. XALATAN has potential hazardous pharmacological effects with respect to the course of pregnancy, to the unborn or the neonate, and should therefore not be used in pregnancy.
Lactation
The safety in lactation has not been established.
Benzalkonium chloride
As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride-preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required.
Caution should be exercised in the use of benzalkonium chloride-preserved topical medication over an extended period in patients with extensive ocular surface disease.

DOSAGE AND DIRECTIONS FOR USE:
Recommended dosage for adults (including the elderly):
Recommended therapy is one eye drop in the affected eye(s) once daily. Optimal effect is obtained if XALATAN is administered in the evening.
Dosage should not exceed more than once daily administration, since more frequent administration may decrease the intra-ocular pressure lowering effect.
If one dose is missed treatment should continue with the next dose as planned.
Reduction of the intraocular pressure in man starts about three to four hours after administration and maximum effect is reached after 8 to 12 hours. Pressure reduction is maintained for at least 24 hours. XALATAN may be used concomitantly with other topical ophthalmic medicines to lower intraocular pressure. If more than one topical medicine is being used, the medicines should be used at least five minutes apart.
Children:
Safety and effectiveness in children have not been established; therefore the use of XALATAN is not recommended in children.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Most undesirable effects observed relate to the ocular system.
***Very common (>1/10)*:**
EYES: Increase iris pigmentation; slight foreign body sensation; eyelash changes.
***Common (>1/100 and <1/10)*:**
EYES: mild to moderate conjunctival hyperaemia; transient punctate epithelial erosions, mostly without symptoms.
***Uncommon (>1/1000 and <1/100)*:**
SKIN: Skin rash
***Rare (<1/1000)*:**
EYES: Iritis/uveitis; macular oedema; symptomatic corneal oedema and erosions; periorbital eodema; darkening of the palpebral skin.

RESPIRATORY: Asthma; asthma aggravation and dyspnoea.
XALATAN has caused increased pigmentation of the iris - see "Warnings".
Macular oedema including cystoid macular oedema has been reported infrequently during XALATAN treatment, mainly in patients with aphakia and pseudophakia with torn posterior lens capsule or anterior chamber lenses.
Systemic events:
The most common systemic adverse events seen with XALATAN were upper respiratory tract infection, colds and flu; pain in muscle, joints, back, chest pain and angina pectoris has also been reported.

Precautions:

General:
Latanoprost is hydrolysed in the cornea. The effect of continued administration of XALATAN in the corneal epithelium has not been fully evaluated.
Asthma:
There is limited experience in patients with asthma, but cases of asthma, asthma aggravation, acute asthma attack, coughing and dyspnoea have been reported.
There is limited experience of XALATAN in inflammatory ocular conditions, inflammatory, neovascular, angle closure, congenital or pigmentary glaucoma and also in pseudophakic patients with open angle glaucoma.
XALATAN has no or little effect on the pupil but there is no experience in acute attacks of closed angle glaucoma. Therefore it is recommended that XALATAN should be used with caution in these conditions until more experience is obtained.
XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses.
As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride-preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride-preserved topical medication over an extended period in patients with extensive ocular surface disease.
XALATAN has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.
There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.
Patients must not let the tip of the dispensing container contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections.

***Information for patients*:**

Patients should be informed about the possibility of iris colour change due to an increase of the brown pigment and resultant cosmetically different eye colouration that may occur when only one eye is treated. Iris pigmentation changes may be more noticeable in patients with green-brown, blue-brown, grey-brown or yellow-brown irises. The onset of the change is usually within the first 8 months of treatment but may occur later in a small number of patients. The effect, based on evidence from consecutive photographs, has been seen in 30% of all patients during 4 years of treatment in clinical trials. The highest incidence was found in patients with green-brown and yellow-brown irides. In patients with homogenously blue, grey, green or brown eyes, the change has only rarely been seen.
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause common ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.
Patients also should also be advised that if they develop an intercurrent ocular condition (e.g. trauma or infection) they should immediately seek their physician's advice concerning the continued use of the multidose container they have been using.
Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Effects on ability to drive and use machines:

Instillation of eye drops may cause transient blurring of vision.

Interactions with other medicines:

Pivotal studies demonstrated that XALATAN is effective as monotherapy.
The intraocular pressure reducing effect of latanoprost has been shown to be additive to that of beta-adrenergic antagonists (timolol).
In short term studies (up to 2 weeks) the effect of latanoprost was additive in combination with adrenergic agonists (dipivefrin), and oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists (pilocarpine).
In case of combined therapy the eye drops should be administered with an interval of at least five minutes.

Incompatibilities:

In vitro studies have shown that precipitation occurs when eye drops containing thiomersal are mixed with XALATAN. If such drugs are used the eye drops should be administered with an interval of at least five minutes.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Apart from ocular irritation and conjunctival hyperaemia, no other ocular side effects are known if XALATAN is overdosed.
If XALATAN is accidentally ingested the following information may be useful:

One bottle contains 125 micrograms latanoprost. More than 90% is metabolised during the first pass through the liver. Intravenous infusion of 3 micrograms/kg in healthy volunteers induced no symptoms but a dose of 5,5-10 micrograms/kg caused nausea, abdominal pain, dizziness, fatigue, hot flushes and sweating.
In monkeys latanoprost has been infused intravenously in doses of up to 500 micrograms/kg without major effects on the cardiovascular system. Intravenous administration of latanoprost in monkeys has been associated with transient bronchoconstriction. However, in patients with moderate bronchial asthma, bronchoconstriction was not induced by latanoprost when applied topically to the eyes in a dose of seven times the clinical dose of XALATAN.
If overdosage with XALATAN occurs, treatment should be symptomatic.

IDENTIFICATION:
The solution is a clear, colourless liquid.

PRESENTATION:
The drops are available in a 5 ml colourless, transparent polyethylene bottle, with a dropper applicator, protected with an inner screw cap, and a tamper-evidentovercap of polyethylene.
Each bottle contains 2,5 ml eye drop solution corresponding to approximately 80 drops.

STORAGE INSTRUCTIONS:
Store in a refrigerator at 2°C - 8°C. Protect from light.
Once the container is opened the contents must be used within 30 days and may be stored at room temperature up to 25°C.
After opening, the container must be stored in the carton.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
31/15.4/0614

NAME AND ADDRESS OF APPLICANT:
Pharmacia South Africa (Pty) Limited
Alphen West G
George Street
Midrand
1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
15 November 2002

New addition to this site: February 2005
Source: Pharmaceutical Industry

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